

Decision Memo for Glycated Hemoglobin/Glycated Protein (Addition of ICD-9-CM 271.3, Intestinal disaccharidase deficiencies and disaccharide malabsorption) (CAG-00336N)

Decision Summary

CMS received an external request to add ICD-9-CM 271.3, Intestinal disaccharidase deficiencies and disaccharide malabsorption, as a covered indication for the Glycated Hemoglobin/Glycated Protein NCD at 190.21 of the NCD Manual

CMS has determined that ICD-9-CM diagnosis code 271.3, Intestinal disaccharidase deficiencies and disaccharide malabsorption, does not flow from the existing narrative for conditions for which a glycated hemoglobin/glycated protein test is reasonable and necessary. CMS will not modify the list of "ICD-9-CM Codes Covered by Medicare Program" in the NCD for Glycated Hemoglobin/Glycated Protein. Intestinal disaccharidase deficiencies will remain on the ICD-9-CM Codes that Do Not Support Medical Necessity list, and providers seeking coverage for the clinical laboratory diagnostic test may continue to submit additional documentation to support a determination of medical necessity.

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Decision Memo

This coding analysis does not constitute a national coverage determination (NCD). It states the intent of the Centers for Medicare & Medicaid Services (CMS) to issue a change to the list of ICD-9-CM Codes Covered that are linked to one of the negotiated laboratory NCDs. This decision will be announced in an upcoming recurring update notification in accordance with CMS Pub 100-4, Chapter 16, Section 120.2 and will become effective as of the date listed in the transmittal that announces the revision.

TO: Administrative File: CAG – 336L Glycated Hemoglobin/Glycated Protein (Addition of ICD-9-CM 271.3, Intestinal disaccharidase deficiencies and disaccharide malabsorption)

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SUBJECT: Addition of ICD-9-CM 271.3, Intestinal disaccharidase deficiencies and disaccharide malabsorption
DATE: October 19, 2006

I. Decision

CMS received an external request to add ICD-9-CM 271.3, Intestinal disaccharidase deficiencies and disaccharide malabsorption, as a covered indication for the Glycated Hemoglobin/Glycated Protein NCD at 190.21 of the NCD Manual

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II. Background

Protein Glycation Assays

Proteins in the blood can be glycosylated post-translationally in a multi-step, non-enzymatic reaction between glucose and the amino groups (or N-terminal) on the protein (Goldstein 2004). The formation of the intermediate Schiff base is reversible whereas the subsequent Amadori rearrangement to a ketoamine product is not. This quality permits the glycosylated products to be assayed as a measure of mean glycemic control. The glycosylated proteins that are typically measured are hemoglobin contained in erythrocytes and serum proteins, primarily albumin. The time at which an equilibrium value can be obtained reflects the turn-over time of the underlying proteins or heme protein being glycosylated (Beach, Goldstein 1994, Schleider, Tahara).

Total glycosylated hemoglobin consists of glycosylated beta chains of hemoglobin A1 (HbA1) and other hemoglobin-glucose products including glucose-lysine adducts and glucose-amino terminus valine adducts on the alpha chain. HbA1 is comprised of HbA1a, HbA1b, and HbA1c. HbA1c comprises 80% of HbA1. Measurement of HbA1c levels is the most common glycosylated hemoglobin assay. HbA1c levels do not correlate directly with total glycosylated hemoglobin levels. The National Glycohemoglobin Standardization Program (NGSP) certifies laboratories because of the problems associated in performing these assays (Goldstein 2004, NGSP website). Assay methods use either charge differences or structural differences between glycosylated and non-glycosylated products. Examples of the former include agar gel electrophoresis and cation-exchange chromatography. Examples of the latter include boronate affinity chromatography and immunoassay. The utility of HbA1c in predicting some aspects of retinopathic disease progression was demonstrated by the Diabetes Complications and Control Trial and United Kingdom Prospective Diabetes Study (DCCT, UKPDS).

Serum protein glycation is typically measured with a fructosamine assay. The original assay measured the reducing power of the serum under alkaline conditions (Johnson). The compound, nitroblue tetrazolium, is reduced to a tetrazinoly radical. Ultimately a formazan dye for a colorimetric assay is produced (Eadie). Some of the newer assays digest the proteins and utilize ketoamine oxidase for oxidation of ketoamine bonds. The hydrogen peroxide that is formed is measured with a Trinder endpoint colorimetric reaction (Wang). The utility of these assays in diabetes management is less established; the prognostic value of fructosamine has not been validated in long-term complication prevention trials (ADA position statement).

Glycosylated hemoglobin assays are used to determine mean glycemic control in a known diabetic patient over a period of 4 to 12 weeks (Beach, Goldstein 1994, Tahara). (It is not a primary screening tool [ADA expert committee 1997, 2003].) Typically, such testing is undertaken every 3 months, at which time equilibrium has been reached. More frequent assessment may be appropriate when there has been an intercurrent event (e.g., glucocorticoid therapy or surgery with immobilization and intravenous fluids) or when trends of interval responses to changes in diabetic management are sought. By contrast, assays of glycosylated proteins in the serum or plasma are used to determine glycemic control over a period of 1-2 weeks (Armbruster, Schleicher). The assay may be used when rapid assessment of the response to a treatment intervention is sought. Although serial use of these assays during pregnancy have been proposed, the effect of hydremic (excess water in blood) states and known declines during pregnancy complicate its use (Hartland 1999, 2000).

These assays are most reliable in the normal or elevated ranges. They are not well validated in the subnormal range. A subnormal value might suggest persistent or repeated hypoglycemia from inappropriate hyperinsulinemia (insulinoma, nesidioblastosis, or other tumor secreting insulin-like peptides), uncompensated malnutrition, or rapid protein/heme turnover. The assay, however, would not be diagnostic.

Disaccharidases

Polysaccharides, e.g., starch, cellulose, and dextrose, are complex carbohydrate structures composed of 10 or more simple sugars, e.g., deoxyribose, fructose, galactose, glucose (dextrose), ribose, and xylose, glycosidically joined with a condensation reaction and the elimination of a water molecule. Oligosaccharides consist of 2 to 9 monosaccharide (simple sugar) residues. Disaccharides are oligosaccharides composed of 2 monosaccharides. Examples of disaccharides include cellobiose (glucose + glucose), lactose (glucose + galactose), maltose (glucose + glucose), sucrose (fructose + glucose), and trehalose (glucose + glucose). The predominant dietary sugars are fructose, glucose, and sucrose (table sugar).

Most sugars cannot be absorbed by diffusion or specialized transport across the oral or intestinal membrane until they have been digested into monosaccharides (Dahlqvist, Miller, Southgate). Disaccharidases are the enzymes that hydrolyze disaccharides. These disaccharidases are specific to the disaccharide, but more than 1 enzyme may hydrolyze a disaccharide. These intracellular enzymes reside primarily in the intestinal brush border region. Disease results when these enzymes are absent or present in reduced amounts. Such deficiencies are termed primary when the defect appears to be congenital and hereditary. Secondary disaccharide deficiencies also occur when intestinal architecture/function is disturbed by another primary disease, e.g, celiac sprue, giardiasis, or radiation enteritis. The most common disaccharidase deficiency is lactose intolerance in teens and adults (Montgomery, OMIM 223100 website). Genetic polymorphisms that might contribute to autosomal dominant persistence of lactase activity into adulthood have been identified, but the role of genetic testing remains to be established (Enattah, Olds). Congenital lactose intolerance is a rare autosomal recessive disease (Hereditary Disaccharide Intolerance Type II) (OMIM 223000 website). Five mutations in the coding region of the lactase gene have been identified (Jarvela, Kuokkanen). Sucrase-Isomaltase deficiency (Hereditary Disaccharide Intolerance Type I), with complete absence of sucrase activity and reduced maltase activity, is a rare autosomal recessive disease (OMIM 609845 website). Several mutations have been reported (OMIM 609845 website).

Malabsorption of a disaccharide is characterized by cramping and fermented feces (Holzel, Weijers 1950, 1961). Intestinal flora acts on the undigested sugar to produce carbon dioxide, hydrogen, methane, and short chain fatty acids. Osmotic forces further contribute to the diarrhea. More severe cases can be accompanied weight loss from malnutrition and acidosis. Occasionally, both lactase and sucrase-isomaltase deficiencies result in hypercalcemia via an unknown mechanism (Belmont, Saarela, Starnes). Symptoms abate when the offending disaccharide is eliminated from the diet. Hypoglycemia is a putative side effect that could occur with profound malabsorption, but it is not reported with naturally occurring disaccharidase deficiencies. Hypoglycemia has been reported with alpha-glucosidase inhibitors used for diabetes management, e.g., acarbose and miglitol. These agents are contraindicated in patients with Type 1 diabetes and intestinal disorders (PDR-drug labels).

The diagnostic test of choice for these disorders is the 3 hour hydrogen breath test after an overnight fast and a disaccharide challenge (Heyman, Karcher, Kastin). Two hour challenge tests using disaccharide and serial measurements of plasma glucose levels. Small bowel biopsies may be used for assays of enzyme activity, to confirm consistent histology, and to exclude other primary intestinal disease (Phillips). Enzyme levels in intestinal fluid can also be measured.

In theory, an intestinal disaccharidase deficiency and the subsequent disaccharide malabsorption could lead to hypoglycemia. A diet replete with glucose as a monosaccharide or from other disaccharides, however, appears to compensate for specific disaccharidase deficiencies. Diabetic patients, particularly Type 1 patients with poor insulin and glucagon counter-regulatory reserve, may not be able to utilize exogenous glucose or to access endogenous hepatic glucose. Hypoglycemia could occur in diabetic patients with disaccharidase deficiency due to primary disease, secondary disease, or iatrogenic complications from oligosaccharidase inhibitors.

III. History of Medicare Coverage

In accordance with section 4554 of the Balanced Budget Act of 1997, CMS entered into negotiations with the laboratory community regarding coverage and administrative policies for clinical diagnostic laboratory services. As part of these negotiations, CMS promulgated a rule that included 23 NCDs. The rule was proposed in the March 10, 2000 edition of the Federal Register (65 FR 13082) and finalized on November 23, 2001 (66 FR 58788). Because the final rule delayed implementation of the NCDs for 12 months, the NCDs became effective on November 25, 2002.

The negotiating committee assembled and reviewed the scientific literature. CMS determined which specific tests were reasonable and necessary and the medical indications for which the laboratory tests were reasonable and necessary. The laboratory NCDs contain a narrative describing these indications. A companion listing of the ICD-9 codes that designates these diagnoses/conditions is entitled "ICD-9-CM Codes Covered by Medicare". A second list, entitled "ICD-9-CM Codes Denied" delineates the diagnosis codes that are never covered by Medicare. A third list, entitled "ICD-9-CM Codes That Do Not Support Medical Necessity" describes codes that generally do not support a decision that the test is reasonable and necessary, but for which there are limited exceptions. Tests in this third category may be covered when they are accompanied by additional documentation.

IV. Timeline of Recent Activities

On July 20, 2006, CMS, in response to an external request, opened a coding analysis item regarding the addition of ICD-9-CM 271.3 to the covered indication code list for the Glycated Hemoglobin/Glycated Protein NCD. CMS posted a tracking sheet to the Internet at <http://www.cms.hhs.gov/mcd/viewtrackingsheet.asp?id=189> and solicited public comment for 30 days on the appropriateness of adding code 271.3 to the list of covered codes for the Glycated Hemoglobin/Glycated Protein NCD.

CMS received no public comments during the comment period, which ended August 19, 2006.

V. General Methodological Principles

During the negotiation meetings that led to the development of the 23 clinical diagnostic laboratory NCDs, CMS stated its intent that the narrative of the NCDs reflect the substance of the determinations. The addition of the coding lists was intended as a convenience to the laboratories and to ensure interpretive consistency by the Medicare claims processing contractors. As such, the codes in the covered code list must flow from the narrative indications of the NCD. This position was reiterated in the November 23, 2001 final rule (66 FR 58795) and in subsequent implementing instructions (Program Memorandum AB-02-110).

On February 25, 2005, CMS announced, in a final notice in the Federal Register (70 FR 9355), that it would maintain the accuracy of the coding lists without substantive changes to the narrative policy through an abbreviated process that did not require scientific evidence. This abbreviated process is called the Coding Analysis for Laboratories (CAL).

VI. CMS Analysis

The "ICD-9-CM Codes Covered by Medicare" list is intended to contain only those codes that flow from the narrative of the indication in the NCD. The Glycated Hemoglobin/Glycated Protein NCD narrative includes the following indications:

Glycated hemoglobin/protein testing is widely accepted as medically necessary for the management and control of diabetes. It is also valuable to assess hyperglycemia, a history of hyperglycemia or dangerous hypoglycemia. Glycated protein testing may be used in place of glycated hemoglobin in the management of diabetic patients, and is particularly useful in patients who have abnormalities of erythrocytes such as hemolytic anemia or hemoglobinopathies.

Intestinal disaccharidase deficiency and disaccharide malabsorption do not describe diabetes, hyperglycemia, a history of hyperglycemia or dangerous hypoglycemia. CMS therefore cannot conclude that the diagnoses of intestinal disaccharidase deficiencies and disaccharide malabsorption (ICD-9-CM 271.3) flow from the NCD narrative.

In the rare instance of a diabetic beneficiary who has concomitant intestinal disaccharidase deficiency as well as a grossly inadequate dietary intake of monosaccharides, the beneficiary would qualify for the glycated hemoglobin or glycated protein laboratory testing on the basis of the diabetes diagnosis rather than on the basis of intestinal disaccharidase deficiency.

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Bibliography

1. Goldstein DE, Little RR, Lorenz RA, Malone JJ, Nathan D, Peterson CM, Sacks DB. Tests of glycemia in diabetes. *Diabetes Care*. 2004;27:1761-73.
2. Maillard LC. Reaction generale des acides amines sur les sucres: ses consequences biologues. *C R Acad Sci*. 1912;154:66-8.
3. Beach KW. A theoretical model to predict the behavior of glycosylated hemoglobin levels. *J Theor Biol*. 1979;81:547-61.
4. Goldstein DE, Little RR, Wiedmeyer HM, England JD, Rohlfing CL. Glycated haemoglobin estimation in the 1990s: a review of assay methods and clinical interpretation. In *Diabetes Annual*. Vol 8. Marshall SM, Home PD, Eds. Amsterdam, Elsevier, 1994, p193-212.
5. Schleicher ED, Olgemoller B, Wiedenmann E, Gerbitz KD. Specific glycation of albumin depends on its half-life. *Clin Chem*. 1993;39:625-8.
6. Tahara Y, Shima K. The response on GHb to stepwise plasma change over time in diabetic patients. *Diabetes Care*. 1993;16:1313-4.

7. NGSP www.missouri.edu/~diabetes/ngsp.html.

8. DCCT Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329:977-86.

9. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352:837-53.

10. Johnson RN, Metcalf PA, Baker JR. Fructosamine: a new approach to the estimation of serum glycoprotein. An index of diabetic control. *Clin Chim Acta*. 1983;127:87-95.

11. Eadie MJ, Tryrer JH, Kukums JR, Hooper WD. Aspects of tetrazolium salt reduction relevant to quantitative histochemistry. *Histochimie*. 1970;21:170-80.

12. Wang Y, Dou C, Yuan C, Datta A. Development of an automated enzymatic assay for the determination of glycated serum protein in human serum. *Clin Chem*. 2005;51:1991-2.

13. American Diabetes Association. Tests of glycemia in diabetes (Position Statement). *Diabetes Care*. 2004;27:S91-4.

14. The expert committee on the diagnosis and classification of diabetes mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care*. 1997;20:1183-97.

15. The expert committee on the diagnosis and classification of diabetes mellitus. Follow-up report on the diagnosis of diabetes mellitus. 2003;26:3160-7.
16. Armbruster DA. Fructosamine: structure, analysis, and clinical usefulness. Clin Chem. 1987;33:2153-63.
17. Hartland AJ, Smith JM, Clark PMS, Webber J, Chowdhury T, Dunne F. Establishing trimester and ethnic group-related reference ranges for fructosamine and HbA1c in non-diabetic pregnant women. Ann Clin Biochem. 1999;36:235-7.
18. Hartland AJ, Smith JM, Dunne F. Correcting serum fructosamine concentration for total protein or albumin concentration is not appropriate during Asian pregnancy. 2000;292:175-80.
19. Dahlqvist A, Borgstrom B. Digestion and absorption of disaccharides in man. Biochem J. 1961;81:411-8.
20. Miller D, Crane RK. The digestive function of the epithelium of the small intestine. I. An intracellular locus of disaccharides and sugar phosphate ester hydrolysis. II. Localization of disaccharide hydrolysis in the isolated brush border portion of intestinal epithelial cells. Biochem Biophys Acta. 1961;52:281-298.
21. Southgate DA. Digestion and metabolism of sugars. Am J Clin Nutrition. 1995;62:203S – 211S.
22. Montgomery RK, Buller HA, Rings EHM, Grand RJ. Lactose intolerance and the genetic regulation of intestinal lactase-phlorizin hydrolase. FASEB J. 1991;5:2824-32.
23. Enattah NS, Sahi T, Savilahti E, Terwilliger JD, Peltonen L, Jarvela I. Identification of a variant associated with adult-type hypolactasia. Nature Genet. 2002;30:233-7.

24. Olds LC, Sibley E. Lactase persistence DNA variant enhances lactase promoter activity in vitro: functional role as a cis regulatory element. *Hum Molec Genet.* 2003;12:2333-40.

25. OMIM 223000 www.genome.ad.jp/dbget-bin/www_bget?omim+223000. Accessed October 2, 2006.

26. Jarvela I, Enattah NS, Kokkonen J, Varilo T, Savilahti E, Peltonen L. Assignment of the locus for congenital lactase deficiency to 2q21, in the vicinity of but separate from the lactase-phlorizin hydrolase gene. *Am J Hum Genet.* 1998;63:1078-85.

27. Kuokkanen M, Kokkonen J, Enattah NS, Ylisaukko-oja T, Komu H, Varilo T, Peltonen L, Savilahti E, Jarvela I. Mutations in the translated region of the lactase gene (LCT) underlie congenital lactase deficiency. *Am J Hum Genet.* 2006;78:339-44.

28. OMIM-223100 www.genome.ad.jp/dbget-bin/www_bget?omim+223100. Accessed October 2, 2006.

29. OMIM-609845 www.genome.ad.jp/dbget-bin/www_bget?omim+609845. Accessed October 2, 2006.

30. Holzel A, Schwartz V, Sutcliffe KW. Defective lactose absorption causing malnutrition in infancy. *Lancet.* 1959;1:1126-8.

31. Weijers HA, van der Kamer JH, Kossel DAA, Dicke WK. Diarrhea caused by deficiency of sugar-splitting enzymes. *Lancet.* 1960;1:296-7.

32. Weijers HA, van der Kamer JH. Diarrhea caused by deficiency of sugar-splitting enzymes. I Acta Paediat. 1961;50:55-71.
33. Belmont JW, Reid B, Taylor W, Baker SS, Moore WH, Morriss MC, Podrebarac SM, Glass N, Schwartz ID. Congenital sucrase-isomaltase deficiency presenting with failure to thrive, hypercalcemia, and nephrocalcinosis. BMC Pediatrics. 2002;2:4-11.
34. Saarela T, Simila S, Koivisto M. Hypercalcemia and nephrocalcinosis in patients with congenital lactase deficiency. J Pediatr. 1995;127:920-3.
35. Starnes CW, Welsh JD. Intestinal sucrase-isomaltase deficiency and renal calculi. N Eng J Med. 1970;282:1023-4.
36. 2006 Physicians Desk Reference. Drug label for acarbose. Murray L, Ed. Montvale, NJ, Thompson PDR, 2006, p 776-8.
37. 2006 Physicians Desk Reference. Drug label for miglitol. Murray L, Ed. Montvale, NJ, Thompson PDR, 2006, www.drugs.com/pdr/miglitol.html. Accessed October 3, 2006.
38. Phillips AD, Avigad S, Sacks J, Rice SJ, France NE, Walker-Smith JA. Microvillous surface area in secondary disaccharidase deficiency. Gut. 1980;21:44-8.
39. Heyman MB, Committee on Nutrition. Lactose intolerance in infants, children, and adolescents. Pediatrics. 2006;118:1279-86.

40. Karcher RE, Truding RM, Stawick LE. Ann Clin Lab Sci. 1999;29:1-8.

41. Kestin DA, Buchman AL. Malnutrition and gastrointestinal disease. Curr Opin Clin Nutr Metab Care. 2002;5:699-706.

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